UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,152	07/23/2003	David B. Agus	67789-19	1369

50670 7590 04/17/2006

DAVIS WRIGHT TREMAINE LLP
865 FIGUEROA STREET
SUITE 2400
LOS ANGELES, CA 90017-2566

EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 04/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/625,152	AGUS, DAVID B.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34 and 57-62* is/are pending in the application.

4a) Of the above claim(s) *10,21 and 29-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-20,22-28 and 57-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/31/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formalities

1. Acknowledgement is made of Applicant's Response to Office Action dated 8/25/2005.

2. Claims 1-9, 11-20, 22-28, and 57-62 are pending in the instant application and are the subject of this Office Action. Claims 1, 12, 23, 26, 29, and 32 are currently amended, Claims 10, 21, and 29-34 have been withdrawn, and Applicant has canceled Claims 35-56 per Response dated 12/05/2005.

3. New Claims 57-62 were added in Applicant response dated 12/05/2005. The newly added claims will only be examined inasmuch as they are drawn to the elected species wherein R_5 is –C=O.

Claim Objections

4. Claims 1-9,12-20, 57-58, and 60-61 are objected to as containing non-elected subject matter. Applicant elected, with traverse, the species wherein R_5 is –C=O in the reply filed on July 11, 2005.

5. In light of Applicant's response dated 12/05/2005, the previous objection to Claims 23-25 and 27-28 is withdrawn.

Claim Rejections - 35 USC § 112 – Second Paragraph

6. Based upon Applicant's amendments in Response dated 12/05/2005, the previous rejection of Claims 1-9, 11-20, and 22-28 under 35 U.S.C. § 112, Second Paragraph is withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-9, 11-20, 22-28, and 57-62 rejected under 35 U.S.C. 102(e) as being anticipated by Steiner et al. (U.S. Patent No. 6,632,447; Issued Oct. 14, 2003, Filed Nov. 8, 2000).

Steiner et al. teach the use of antiestrogens for the chemoprevention and treatment of prostate cancer (see especially Column 2, Lines 61-67). Absent any teaching in the reference to the contrary, the term "prostate cancer" as used therein is taken to mean both androgen-dependent and independent prostate cancer as the traditional use of the term "prostate cancer" as used in the art encompasses any and all types of prostate cancer. The word "treatment" as used in the reference is taken to

mean a method that suppresses or inhibits tumor metastasis and/or primary tumor size, as this is traditionally the intended meaning of the word as it pertains to cancer.

The reference further teaches the administration of antiestrogens, specifically selective estrogen receptor modulators (SERMs), in a method of treating a subject with prostate cancer (see Column 3, Lines 1-6 and 14-15). The reference goes on to teach that the chemopreventative/treatment agent can be raloxifene (see especially Column 4, Lines 7-8) thus teaching the limitations of Claims 1, 9, 11, 23, and 57-59.

The compositions and methods of Steiner et al. can be administered orally (see Column 6, Lines 10-18) in doses ranging from 5-80 mg/day, specifically 60 mg/day (see especially Column 6, Lines 18-29) thus teaching the limitations of Claims 2-3, 8, and 24.

The invention of the reference includes the use of the compounds and their analogs, derivatives, intermediates, isomers, and metabolites (see especially Column 5, Lines 7-12), thus teaching the limitations of Claims 12-14, 19-20, 22, 26-27, and 60-62.

Thus, the reference teaches all of the limitations of Claims 1-3, 8-9, 11-14, 19-20, 22-24, 26-27, and 57-62.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Applicant's arguments filed 12/05/2005 have been fully considered but they are not persuasive. Claims 1-9, 11-20, and 22-28 stand rejected under 35 U.S.C. § 103(a) as being obvious over Lau et al. (Cancer Research, 60:3175-3182, 2000), hereinafter "Lau", in further view of Neubauer et al. (The Prostate, 27:220-229, 1995), hereinafter "Neubauer".

The instant Claims are drawn to a method of treating androgen-independent prostate cancer in a mammal comprising the administration of a compound having the formula recited in Claim 1.

The first prior art reference (Lau et al.) states that estrogen receptors α and β are expressed in normal and malignant prostatic epithelial cells (see Abstract). Lau et al. state that the androgenindependent prostate cancer cell lines DU145 and PC3 both express ERβ. Lau et al. do not discuss the administration of an antiestrogen compound of the formula recited in instant Claim 1 in the treatment of androgen-independent prostate cancer, however they do describe the potential of antiestrogens as prostate cancer therapies wherein they discuss the growth-inhibitory action of antiestrogens on PC3 and DU145 cells (see Abstract).

The second prior art reference (Neubauer et al.) describes how the antiestrogen raloxifene (LY156758) produced significant inhibition of PAIII metastasis from the primary tumor in the tail of a rat and suggests or motivates that further studies are needed to define the maximal antitumor efficacy and the mechanism of action of raloxifene in urogenital solid tumor models. The reference goes on to state that: "Inasmuch as the metastatic processes in the rat PAIII model may be similar to human

urogenital malignancies, raloxifene deserves consideration for clinical evaluation in humans" (see especially pg. 228, last paragraph).

Thus, it would have been obvious to one skilled in the art at the time the invention was made to further evaluate raloxifene in models of androgen-independent prostate cancer with a possible mechanism being inhibition of ERβ. The skilled artisan would be led to evaluate raloxifene in other models of androgen-independent prostate cancer as well as to use higher doses and different treatment regimes than those used by Neubauer given the known existence of ERβ in androgen-independent prostate tissue as discussed in Lau et al. and the evidence of inhibition of prostate cancer metastasis by raloxifene as taught by Neubauer.

It should be noted that the primary reference only used a maximum dose of 20 mg/kg/day with no signs of toxicity over a 28-day treatment schedule. The weight of the rats used in the model was 0.110 to 0.125 kg. Thus, the maximum dosage administered was only 2.2 mg/day. Applicant claims doses of 10 – 300 mg/day, preferably 60 mg/day, which are 5 – 130x more than the dose administered by the reference. Given the evidence presented by Neubauer that raloxifene can inhibit prostate cancer metastasis at only 2.2 mg/day, it would have been obvious to the skilled artisan to increase the dosage administered, even up to the LD_{50} of raloxifene in rats. The LD_{50} of raloxifene in rats is 5000 mg/kg (orally) and greater than 2000 mg/kg *i.p.* (see MSDS of Raloxifene, Eli Lilly). Clearly, Neubauer administered raloxifene at nowhere near the median lethal dose. Thus, it would have been obvious to one skilled in the art to increase the dose and/or treatment schedule (e.g. 20 mg/kg, 3x/day; 60

mg/kg/day) to treat androgen-independent prostate cancer as claimed in the instant invention.

Applicant's argument that Neubauer's disclosure provides evidence of nonobviousness is not persuasive. As stated above, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the doses, schedule of treatment, and models of the reference to further investigate the teachings therein. This is especially true given that Neaubauer explicitly states, in more than one instance, that raloxifene should be further studied and represents a class of compounds with potential efficacy in the treatment of hormone-insensitive human prostatic cancer.

To address Applicant's arguments against obviousness of the instant claims, three basic criteria must be met to establish the *prima facie* case of obviousness as presented above: (1) "there must be some *suggestion* or motivation...to modify the reference," (emphasis added); (2) "there must be a *reasonable* expectation of success," and (3) the prior art references "must teach or *suggest* all the claim limitations." (MPEP § 2145(X)(A).

I. Suggestion or Motivation to Modify Reference

Applicant has argued that Neubauer provides evidence of *nonobviousness* of the present inventive methods. This argument, however, is not persuasive. The fact that the reference states raloxifene, at the dosage used and in that particular model and treatment schedule, did not inhibit tumor growth does not teach away from further studies using higher doses or different treatment schedules to treat androgen-

independent prostate cancer. In fact, as presented above, Neubauer explicitly states that: "Inasmuch as the metastatic processes in the rat PAIII model may be similar to human urogenital malignancies, raloxifene deserves consideration for clinical evaluation in humans" (see especially pg. 228, last paragraph). In the Abstract, the reference states: "Further studies are needed to define the maximal antitumor efficacy and the mechanism of action of raloxifene in urogenital solid tumor models. These data support the contention that raloxifene represents a class of active antimetastatic agents with potential efficacy in the treatment of hormone-insensitive human prostatic cancer" (see Abstract). Thus, there is clearly a motivation to modify the teachings of the reference. That motivation is suggested in the reference as stated above and one of ordinary skill in the art at the time the invention was made would be inclined to use higher doses given that a dose of 2.2 mg/day elicited an antimetastatic response.

Applicant has further argued that Neubauer mischaracterized and misunderstood the pathophysiology of the disease and the effect of the drug and therefore taught away from the present invention. However, it should be noted that the reference teaches possible mechanisms of the drug's affect on metastasis, not tumor suppression. In fact, estrogen receptor β (ERβ) was not identified as being present in the prostate until 1-2 years after Neaubauer's publication (see especially Kuiper et al, 1996 and Kuiper et al, 1997). Thus, the reference could not have postulated this possible mechanism of action, as it was not yet known to be a possibility.

II. There is a Reasonable Expectation of Success

Applicant has argued that Neubauer states that raloxifene did not inhibit tumor growth thus teaching away from a reasonable expectation of success. This argument, however, is not persuasive. Antiestrogens are known in the art. The expression of ERβ in prostate tissue is known in the art as evidenced by the secondary reference (Lau et al.). Neubauer teaches the use of raloxifene, an antiestrogen, in the inhibition of androgen-independent prostate cancer metastasis in one model system and an upper dose of 20 mg/kg administered once a day (*i.e.* 2.2 mg/day). The reference also teaches that further studies are needed to "*define the maximal antitumor efficacy* and mechanism of action" of raloxifene in the treatment of hormone-resistant prostate cancer. Given the above, one skilled in the art would reasonably expect success in modifying the reference model, doses, and administration schedule in the treatment of androgen-independent prostate cancer. In addition, given that the instant claims are drawn to a method of treating androgen-independent prostate cancer, no unobviousness is seen in using a higher dose when the reference has shown that a low dose (2.2 mg/day) reduces metastasis of the primary tumor.

III. The Reference Suggests All of the Claim Limitations

Applicant has argued that the reference does not teach or suggest all of the claim limitations. This argument is not persuasive. The reference does not need to explicitly teach all of the limitations of the present claims, only suggest them. The instant claims are drawn to a method of treating androgen-independent prostate cancer using the

antiestrogen, raloxifene. As stated above, Neubauer suggests, and at times explicitly states, that raloxifene should be *studied further to define the maximal antitumor activity.* It is up to the skilled artisan to determine the best method of going about the suggested studies. Reducing the metastasis of a primary tumor is one way to "treat" a given cancer. Thus, the reference teaches the limitation of "treating" as recited in the instant claims. Further, it would have been obvious to one of ordinary skill in the art to use the higher doses as recited in instant Claims 2-5 given that a dose of 2.2 mg/day has been shown to inhibit tumor metastasis.

One skilled in the art at the time the invention was made would know: a) Raloxifene is an antiestrogen; b) Estrogen receptors are present in prostate cancer tissue; c) Raloxifene is known to inhibit metastasis of androgen-independent prostate cancer at a doses of 20 mg/kg/day (2.2 mg/day), and d) Raloxifene at that dose does not stabilize the primary tumor.

Given that knowledge at the time the invention was made, the skilled artisan would be inclined to increase the dosage and/or treatment schedule, use raloxifene in other prostate cancer models, and attempt to elucidate the mechanism of action, as suggested by the reference. Thus, although not teaching the claim limitations explicitly, the reference does suggest them as well as provide a motivation to practice them as described above.

In light of the above response to applicant's arguments, the rejection under 35 U.S.C. § 103(a) is maintained.

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 8:00 am - 6:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James D. Anderson
Examiner
Art Unit 1614

JDA

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600